

WHAT IS CLAIMED IS:

1. An isolated nucleic acid molecule comprising a polynucleotide encoding a phospholipase A2 γ polypeptide. (SEQ ID NO:1)

2. An isolated nucleic acid molecule in accordance with Claim 1, wherein said phospholipase A2 γ polypeptide catalyzes cleavage of fatty acids from the sn-2-position of phospholipids.

3. An isolated nucleic acid molecule in accordance with Claim 2 wherein said polynucleotide encodes a sequence as set forth in SEQ ID NO: 1 or SEQ ID NO:2.

4. A vector comprising a nucleic acid molecule in accordance with Claim 1.

5. A cell transformed or transfected with a vector in accordance with Claim 4.

6. An isolated nucleic acid molecule comprising a fragment of a polynucleotide encoding a phospholipase A2 γ wherein said fragment specifically hybridizes with a sequence as set forth in at least one of SEQ ID NOS 3, SEQ ID NO:4 and SEQ ID NO: 5.

7. An isolated nucleic acid comprising a polynucleotide having at least about 90% identity with SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, or SEQ ID NOS 6, 7, 8 or 9 wherein the encoded polypeptide has or modulates enzymatic activity.

8. An isolated nucleic acid according to claim 7 comprising SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, or SEQ ID NOS 6, 7, 8 or 9.

9. An antisense sequence which specifically hybridizes to SEQ ID NO: 3, or SEQ ID NO:4, SEQ ID NO: 5 or SEQ ID NO: 6.

10. An isolated polypeptide comprising a phospholipase A2 γ .

11. An isolated polypeptide in accordance with Claim 10 which catalyzes cleavage of fatty acids from the sn-2-position of phospholipids.

12. An isolated polypeptide in accordance with Claim 11 which has at least 90% identity with SEQ ID NO: 1 or SEQ ID NO:2.

13. An isolated polypeptide in accordance with Claim 12 comprising SEQ ID NO:1 or SEQ ID NO:2.

14. An isolated polypeptide in accordance with Claim 12 which is a conservatively substituted variant of SEQ ID NO:1 or SEQ ID NO:2.

15. An antibody capable of binding to a phospholipase A₂γ according to Claim 1.

16. A vector comprising a nucleic acid molecule in accordance with Claim 1 suitable for vectoring into a transgenic mouse wherein the reporter gene encodes an enzyme capable of being detected by a colorimetric, fluorometric or luminometric assay.

17. A method in accordance with Claim 16 wherein said reporter gene encodes a luciferase.

18. A method in accordance with Claim 30 comprising administering to the mouse an iPLA₂γ polypeptide as set forth in SEQ ID NO:1, SEQ ID NO:2 or a conservatively substituted variant thereof or administering a polynucleotide encoding said iPLA₂γ polypeptide wherein the repressor binding site comprises SEQ ID NO:10.

19. A genetically engineered cell in accordance with Claim 18 wherein said reporter gene encodes an enzyme capable of being detected by a colorimetric, fluorometric or luminometric assay.

20. A genetically engineered cell in accordance with Claim 19 wherein said reporter gene encodes a luciferase.

21. A method for preparing a transgenic mouse which further comprises breeding a transgenic founder mouse having SEQ ID 1 stably integrated in its genome with WT B6CBAE1/J mice.

22. A transgenic mouse having in its genome a nucleic acid molecule comprising a polynucleotide encoding a phospholipase A₂γ polypeptide. (SEQ ID NO: 1)

23. A transgenic mouse in accordance with Claim 22 wherein said phospholipase A₂γ polypeptide catalyzes cleavage of fatty acids from the sn-2-position of phospholipids.

24. A transgenic mouse in accordance with Claim 23 wherein said polynucleotide encodes a sequence as set forth in SEQ ID NO:1 or SEQ ID NO:2.

25. A vector which can be used to generate a transgenic mouse in accordance with Claim 24.

26. A transgenic mouse having within its genome a nucleic acid molecule comprising a fragment of a polynucleotide encoding a phospholipase A₂γ wherein said fragment specifically hybridizes with a sequence as set forth in SEQ ID NOS:3 or SEQ ID NO:4 or SEQ ID NO:5.

27. A transgenic mouse in accordance with Claim 6 wherein said fragment comprises a polynucleotide having at least about 90% identity with SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, or SEQ ID NOS 6, 7, 8 or 9 wherein the encoded polypeptide has or modulates enzymatic activity.

28. A transgenic mouse having within its genome a nucleic acid according to Claim 7 comprising SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, or SEQ ID NOS:6, 7, 8 or 9.

29. A transgenic mouse in accordance with Claim 8 having within its genome a nucleic acid having an antisense sequence which specifically hybridizes to SEQ ID NO:3, or SEQ ID NO:4, SEQ ID NO:5 or SEQ ID NO:6.

30. A genetically engineered cell in accordance with Claim 31 wherein said repressor binding site comprises SEQ ID NO:10.

31. A mitochondrial targeting sequence MISRLAQFKPSSQILRKΔVS (SEQ ID NO:58) at the N-terminus of the 74kDa iPLA₂γ product.

32. A mitochondrial import signal and cleavage site (LRK/VS) (SEQ ID NO:95) immediately downstream from the 74 kDa alternative start site which directs iPLA₂γ into mitochondria resulting in a truncated protein of approximately 72 kDa.

33. A subcellular localization of iPLA₂γ into both peroxisomes and mitochondria which may have important implications for the role of iPLA₂γ in modulating cellular function.

34. An alternative exon 5 splice variant utilizing gt/ag splice junction and resulting in a novel 5 amino acid change (ASCSV) SEQ ID NO:28.

35. iPLA₂γ exons designated exons 1 (SEQ ID NO:29) and 4 (SEQ ID NO:30) corresponding to genomic sequence 135327-135622 and 125460-125571 of GenBank genomic clone RG054D04.

36. A truncated iPLA₂γ 63kDa (SEQ ID NO: 21) resulting from initiation at methionine number 122 of iPLA₂γ which is expressed in the baculoviral and in vitro expression systems at least 20 fold greater (at the mRNA and protein levels) than the full - length 88kDa (SEQ ID NO: 1) protein product.

37. A transgenic construct containing the γ MHC promoter upstream of the full-length iPLA₂γ coding sequence (SEQ ID NO: 6) for myocardial specific expression of recombinant iPLA₂γ in TGiPLA₂γ mice.

38. A transgenic mouse (TGiPLA₂γ) which expresses 77kDa, 74kDa, 63kDa, and 45kDa isoforms of recombinant human iPLA₂γ.

39. A polypeptide (SEQ ID NO: 1) with alternative ATG start sites encoding 88, 77, 74, and 63kDa iPLA₂γ proteins

40. An in vitro expression construct in which truncated iPLA₂γ sequences (SEQ ID NO: 6, 15, 18, and 21) are cloned downstream from the SV40 promoter of vector pEF.

41. A transcription factor binding region defined by gel shift analysis between nucleotide residues 6-50 encoding the 88 kDa protein and including the sequence 5'-TATTAATCTGACTGTAGATATATATATTTACCTCCTTAGTAATGC-3' (SEQ ID NO:59) within the N-terminal coding region of iPLA₂γ.

42. Three MyoD transcription factor binding sites (E-boxes) defined by the consensus nucleotide sequence CANNTG in promoter 1 (pre exon 1) sequence of the iPLA₂γ gene corresponding to nucleotide residues -22 through -27 corresponding to nucleotide sequence 5'-CAAGTG-3' (SEQ ID NO: 60), -53 through -58 corresponding to nucleotide sequence 5'-CAGGTG-3' (SEQ ID NO:61), and -349 through -354 corresponding to nucleotide sequence 5'-CAGGTG-3' (SEQ ID NO:62) upstream from start of exon 1.

43. An initiator (Inr) sequence with a consensus sequence of Py-Py-A-N-T/A-Py-Py at which nuclear protein constituents bind to 5'-GCG TCA CTT CCG CTG GGG GCG G-3' (SEQ ID NO: 77) at nucleotide residues -54 through -75 upstream from the putative start of exon 2.

44. A pre exon 2 sequence 5'-GCCAGTGTTTG-3' (SEQ ID NO: 78) which is consistent with a CORE promoter element was identified in comparisons of human, mouse, and rat sequence.

45. A transcriptional regulatory domain within the 5' coding region (nucleotide residues 1-315)(SEQ ID NO: 57) of iPLA₂γ.

46. A nuclear binding domain corresponding to SEQ ID NO:59 defined by gel shift analysis within the transcriptional regulatory domain.

47. iPLA₂γ exons SEQ ID NO:29 and 30 corresponding respectively to exons 1 and 4.

48. A novel splice variant X resulting from splicing exon 1 and truncated exon 5 sequence (SEQ ID NO:5).